IN THE UNITED STATES DISTRICT COURT

FOR THE DISTRICT OF DELAWARE

NOVOZYMES A/S,	)	
	)	
Plaintiff,	)	
	)	
v.	)	C. A. No. 05-160-KAJ
	)	
GENENCOR INTERNATIONAL, INC. and ENZYME DEVELOPMENT CORPORATION,	)	
	)	
Defendants.	)	

DEFENDANTS' PROPOSED FINDINGS OF FACT AND CONCLUSIONS OF LAW

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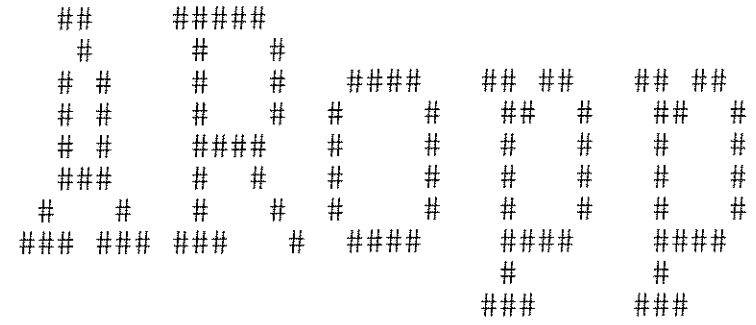

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I. INTRODUCTION

Plaintiff Novozymes A/S ("Novozymes") brought this patent infringement action against Defendants Genencor International, Inc. and Enzyme Development Corporation (collectively, "Genencor"), accusing Genencor of infringing claims 1, 3, and 5 of U.S. Patent No. 6,867,031 (the "'031 Patent"), which issued on March 15, 2005. (Complaint, Docket Item ("D.I.") 1, A-1501–1542.) Genencor denies infringement, and asserts that the '031 Patent is invalid as obvious and for lack of enablement, and that it is unenforceable due to inequitable conduct and prosecution laches. (Amended Answers, D.I. 89, A-1701–1720 and 90.) Novozymes moved for a preliminary injunction, which this Court denied. (Memorandum Order, D.I. 68.) The case has been bifurcated with the issues of damages and willful infringement reserved for a second trial, if necessary. (First Amended Scheduling Order, D.I. 70.)

II. PROPOSED FINDINGS OF FACT

A. The Parties

1. Plaintiff Novozymes A/S is a Danish corporation having a place of business at Krogshoejvej 36, DK-2880 Bagsvaerd, Denmark. (Complaint, D.I. 1 at ¶ 2, A-1501.)

2. Defendant Genencor International, Inc. is a Delaware corporation having its principal place of business at 925 Page Mill Road, Palo Alto, California. (Complaint, D.I. 1 at ¶ 3, A-1501; Amended Answer, D.I. 89 at ¶ 3, A-1702.)

3. Defendant Enzyme Development Corporation is a Delaware corporation having its principal place of business at 21 Penn Plaza, New York, New York. (Complaint, D.I. 1 at ¶ 4, A-1502; Amended Answer, D.I. 90 at ¶ 4.) Enzyme Development Corporation is a United States distributor for Genencor's SPEZYME® Ethyl product. (Updated Proposed Final Pretrial Order, D.I. 101, section III ("Uncontroverted Facts") at ¶ W, A-1144.)

B. **The '031 Patent**

(1) Field of the '031 Patent

4. The '031 Patent is concerned with variants of alpha-amylase enzymes. (Uncontroverted Facts at ¶ D, A-1141.)

5. The '031 Patent discusses, *inter alia*, *Bacillus stearothermophilus* variant alpha-amylases that have been modified by the deletion of the amino acids at positions equivalent to positions 179 and 180, using SEQ ID NO:3 from the '031 Patent for numbering purposes. (Uncontroverted Facts at ¶ Q, A-1143.)

6. One of ordinary skill in the art in the field of the '031 Patent in 1995 had a Ph.D. in protein engineering, molecular biology, or related fields, as well as a few years of post-doctoral experience. (Machius, Tr.[1] at 451:19-452:1, A-5682–5683; Alber, Tr. at 201:3-10, A-5202.)

(2) Alpha-amylases and Proteins

7. Alpha-amylases are proteins. All proteins are chains of amino acids that are joined together by chemical bonds, called "peptide bonds." There are 20 different amino acids that occur in nature, and each protein chain includes many of these 20 amino acids assembled in a particular order. The order of the amino acids in a protein is known as its "amino acid sequence" or its "primary structure." (Uncontroverted Facts at ¶ I, A-1142.)

8. One end of a protein chain of amino acids is called the "N-terminus," and the other end is called the "C-terminus." (Uncontroverted Facts at ¶ J, A-1142.)

9. Scientific nomenclature assigns a one-letter abbreviation to each of the 20 different natural amino acids. The sequence of a particular protein can be specified by writing the one-letter abbreviation for each amino acid in the order that it appears in the protein chain. When a protein is

[1] References to testimony at trial are to the hearing transcript, "[Witness Name], Tr. at ___." References to admitted trial exhibits are to "TE ___." All these materials are included in the parties' Joint Appendix, and are also cited as "A-[page(s)]."

displayed in this form, the N-terminus is typically the left-hand end and the C-terminus is typically the right-hand end. (Uncontroverted Facts at ¶ K, A-1142.)

10. A particular amino acid residue within a sequence can be denoted by giving the single letter abbreviation for the name of the amino acid, followed by a number indicating its position in the amino acid sequence. (Uncontroverted Facts at ¶ L, A-1142.)

(3) Asserted Claims of the '031 Patent

11. Claim 1 of the '031 Patent recites a variant of a parent *Bacillus stearothermophilus* alpha-amylase, wherein the variant has an amino acid sequence that has at least 95% homology to the parent *Bacillus stearothermophilus* alpha-amylase and comprises a deletion of amino acids 179 and 180, using SEQ ID NO:3 for numbering, and wherein the variant has alpha-amylase activity. (Uncontroverted Facts at ¶ R, A-1143.)

12. Claim 3 of the '031 Patent recites a variant alpha-amylase, wherein the variant has at least 95% homology to SEQ ID NO:3 and comprises a deletion of amino acids 179 and 180, using SEQ ID NO:3 for numbering, and wherein the variant has alpha-amylase activity. (Uncontroverted Facts at ¶ T, A-1143.)

13. Claim 5 of the '031 Patent recites a variant of a *Bacillus stearothermophilus* alpha-amylase, wherein the alpha-amylase variant consists of a deletion of amino acids 179 and 180, using SEQ ID NO:3 for numbering. (Uncontroverted Facts at ¶ U, A-1144.)

(4) Protein Engineering

14. A "parent *Bacillus stearothermophilus*" is a wild type (naturally occurring) *Bacillus stearothermophilus* bacterium. (Arnold, Tr. at 137:25-138:7, A-5138–5139, 144:13-18, A-5145.)

15. According to the '031 Patent, a "variant" protein is the product of protein engineering a wild type parent gene. (Arnold, Tr. at 137:23-25, A-5138, 138:8-9, A-5139.) A variant is derived

from its parent. (Alber, Tr. at 202:8-11, A-5203.) Every variant has a parent. (Arnold, Tr. at 137:23-25, A-5138, 138:8-9, A-5139; Alber, Tr. at 202:8-11, A-5203.)

16. "Protein engineering" is human manipulation of a protein sequence by substituting, inserting, and/or deleting amino acids. (Arnold, Tr. at 138:11-20, A-5139.)

17. A protein engineer manipulates the DNA encoding the parent protein (also known as the "gene") to create a variant protein. (Alber, Tr. at 202:12-19, A-5203; Arnold, Tr. at 137:19-139:17, A-5138–5140.)

18. "Post-translational modification" refers to chemical reactions that happen to proteins after they are made, including cleavage (cutting) of the protein chain. (Alber, Tr. at 203:18-24, A-5204, 204:15-21, A-5205.)

19. A skilled protein engineer in 1995 would have considered changes to a protein through post-translational modification to be sequence changes that are relevant to a comparison of two sequences when computing the % homology between those two sequences. (Alber, Tr. at 204:4-205:24, A-5205–5206.) Novozymes' expert Dr. Arnold agrees. (Arnold, Tr. at 176:19-177:13, A-5177–5178.)

C. **The '031 Patent Prosecution History**

(1) Effective Date of the '031 Application

20. The application that issued as the '031 Patent was filed on December 19, 2001. It was filed as a divisional application of application Serial No. 09/902,188, filed July 10, 2001, which was a continuation of application Serial No. 09/354,191, filed on July 15, 1999, which was a continuation of application Serial No. 08/600,656, filed on February 13, 1996, which was a continuation of International Application No. PCT/DK96/00056, filed on February 5, 1996. (TE 100, A-7001–7040.)

21. As described below (FF 186-194[2]), the '031 Patent's support for the term "% homology" includes use of the GAP (GCG) program. That program is not mentioned in any of the four Danish applications to which the '031 Patent claims priority. (TE 101 at 776-1104, A-7816–8144.) Novozymes' earliest-filed application that describes the GAP (GCG) program is the PCT application No. PCT/DK96/00056, filed on February 5, 1996. (TE 101 at 2-3, A-7042–7043.)

22. The first priority application filed on February 3, 1995 does not disclose the amino acid sequence of SEQ ID NO:3 or any *Bacillus stearothermophilus* alpha-amylase. (TE 101 at 766-827, A-7806–7867.) The earliest-filed priority application that discloses SEQ ID NO:3 or any *Bacillus stearothermophilus* alpha-amylase is the application filed on March 29, 1995. (TE 101 at 915-959, A-7955–7999.)

23. Thus, the earliest possible effective filing date for the '031 Patent is March 29, 1995.

(2) Initial Rejection Over Suzuki/Bisgard-Frantzen

24. The United States Patent and Trademark Office (the "PTO") relied upon at least two publications to reject claims during prosecution of the '031 Patent: (i) an article published in the November 15, 1989 issue of the Journal of Biological Chemistry by Yutaka Suzuki *et al.*, titled "Amino Acid Residues Stabilizing a Bacillus α-Amylase against Irreversible Thermoinactivation," ("Suzuki"); and (ii) International Patent Publication No. WO 95/10603 by Henrik Bisgard-Frantzen *et al.*, titled "Amylase Variants" and dated April 20, 1995 ("Bisgard-Frantzen PCT"). (Uncontroverted Facts at ¶ AA, A-1145.)

25. Suzuki describes mutants or variants of the alpha-amylase enzyme *Bacillus amyloliquefaciens* ("BAN"). It discloses that some of these mutant alpha-amylases have improved thermostability compared to the wild type *Bacillus amyloliquefaciens* alpha-amylase from which they were derived. (Uncontroverted Facts at ¶ BB, A-1145.)

[2] References to proposed findings of fact are to "FF ___," and to conclusions of law are to "CL ___."

26. The Bisgard-Frantzen PCT describes alpha-amylase enzymes from three *Bacillus* species: *Bacillus amyloliquefaciens* ("BAN"), *Bacillus stearothermophilus* ("BSG"), and *Bacillus licheniformis* ("BLA"), and teaches that these alpha-amylases have homologous amino acid sequences. (Uncontroverted Facts at ¶ CC, A-1145.)

27. During the prosecution of the '031 Patent, in an Office Action ("OA") dated July 29, 2003, the Examiner issued an obviousness rejection under 35 U.S.C. § 103(a) based on a combination of Suzuki and the Bisgard-Frantzen PCT. (Uncontroverted Facts at ¶ DD, A-1145; TE 101, A-7041–8146.)

28. When making the obviousness rejection, the '031 Patent Examiner stated that "it would have been obvious to one of ordinary skill in the art to introduce the mutations disclosed by Suzuki *et al.* into the corresponding positions of *Bacillus stearothermophilus* [alpha]-amylase in order to produce a homologous [alpha]-amylase which would have been reasonably expected to have similar improved properties in view of the known homology between these [alpha]-amylases." (Uncontroverted Facts at ¶ EE, A-1146.) The Examiner further found that the Bisgard-Frantzen PCT, on which all three '031 patent inventors were named as inventors, taught that Suzuki's positions 176 and 177 in BAA (another abbreviation for *Bacillus* amyloliquefaciens) corresponded to positions 179 and 180 in *Bacillus stearothermophilus*. (Uncontroverted Facts at ¶ EE, A-1146; TE 101 at 588, A-7628; TE 110 at NV-0200005, A-8169.1.)

29. Novozymes did not dispute during prosecution, nor has it disputed during this action, that the Examiner properly found that the '031 claims as they stood on July 29, 2003 were *prima facie* obvious over the combination of Suzuki and the Bisgard-Frantzen PCT.

(3) Novozymes' Internal Plan to "Buy Time" in Prosecution

30. On January 13, 2004, Jason Garbell, a Novozymes' in-house patent attorney, circulated an e-mail message to the '031 Patent inventors, Drs. Torben Borchert, Alan Svendsen, and Henrik

Bisgard-Frantzen, as well as others at Novozymes, commenting on the July 29, 2003 OA. In that e-mail, Mr. Garbell presented a plan he designed to obtain broad claims and avoid the rejection over Suzuki. Mr. Garbell stated that "[t]he famous Suzuki reference (attached) is now an issue again, as it is currently cited by the USPTO as rendering the claims obvious." (TE 110 at NV-0200004 - NV-0200006, A-8169–8170.)

31. In discussing the plan to obtain broader claims, Mr. Garbell and Novozymes characterized the alleged invention of the '031 Patent. Specifically, Mr. Garbell stated that "we are pursuing a double deletion of positions 179 and 180 in SEQ ID NO:3 (*Bacillus stearothermophilus*)." (Borchert, Tr. at 349:8-351:4, A-5580-5582; TE 110 at NV-0200004 – NV-0200005, A-8169–8169.1 (emphasis added.)) Mr. Garbell reviewed the Examiner's obviousness rejection, in conjunction with an internal analysis of Suzuki by Dr. Borchert; he agreed that Suzuki taught the "double deletion" corresponding to positions 179 and 180 in *Bacillus stearothermophilus* and with the Examiner's analysis of the Bisgard-Frantzen PCT reference. (TE 110 at NV-0200005, A-8169.1.)

32. In his January 13, 2004 e-mail, Mr. Garbell set out two options to overcome the rejection of the pending claims. "Option 1" was to provide alleged "unexpected results" over Suzuki: "that is, that a double deletion in *Bacillus stearothermophilus* is surprisingly superior (for thermostability) over the corresponding double deletion in BAA based on comparative testing." "Option 2" was to narrow the claims to require additional alterations not disclosed in Suzuki, such as substitution of a cysteine at residues 349 and 428. (Borchert, Tr. at 349:8-351:4, A-5580–5582; TE 110 at NV-0200004 – NV-0200006, A-8169–8170.) Dr. Borchert received this e-mail and was involved in executing this plan from the beginning. (Borchert, Tr. at 346:5-10, A-5577, 347:9-348:4, A-5578–5579, 352:1-25, A-5583; Garbell, Tr. at 427:2-428:14, A-5658–5659; TE 110 at NV-0200005 – NV-0200006, A-8169.1–8170.)

33. In the January 13, 2004 e-mail, Mr. Garbell stated that Option 2 was not preferable because such claims might not cover a competitor's future product if the product does not have the other alterations required by the claims. (TE 110 at NV-0200005 – NV-200006, A-8169.1–8170.) Novozymes personnel agreed; responding that day to Mr. Garbell, Paul Shenker of Novozymes stated that "[i]f we do not do it [Option 1] GCI [Genencor] may have an easy design around hole." (Borchert, Tr. at 355:8-356:15, A-5586–5587; TE 110 at NV-0200004, A-8169.) Dr. Borchert understood that the narrowed claims created a hole in Novozymes' patent protection, and was concerned that not having patent protection on the 179-180 deletion of BSG would leave room for someone to come in and compete with Novozymes, particularly Genencor, "our main competitor." (Borchert, Tr. at 355:8-356:15, A-5586–5587; TE 110 at NV-0200004, A-8169.) '031 Patent co-inventor Bisgard-Frantzen explained Novozymes' motivations clearly:

> This is a very complicated situation – but more relevant also a VERY important issue to deal with the best possible way, with the best experts involved. Termamyl SC is between top 5 of our most profitable products with a sale > 100mio. Dkr, so it is worthwhile to do an extra effort.

(TE 110 at NV-0200004, A-8169 (emphasis in original.))

34. With respect to Option 1, Mr. Garbell stated in the January 13, 2004 e-mail that:

> [t]here are a few possibilities for what the comparative testing must entail, but I suggest that we compare the double deletion in wild type BAA (with no other changes) to both a wild type *Bacillus stearothermophilus* having the double deletion at positions 179 and 180 and to many other variants of *Bacillus stearothermophilus* that are 80% homologous and have a double deletion at positions 179 and 180. We would need to show that wild type BSG and these variants have improved thermostability over BAA with the corresponding (*sic*) double deletion.

(TE 110 at NV-0200006, A-8170.) Mr. Garbell concluded in the e-mail message that "I believe this case is important to cut off possible design arounds by our competitors." (TE 110 at NV-0200006, A-8170.)

35. In a subsequent, follow-up e-mail message dated January 14, 2004, addressed to the '031 Patent inventors and others at Novozymes, Mr. Garbell set out the requirements for the comparative testing. Mr. Garbell stated that he selected thermostability as the parameter to test "because that is what Suzuki focuses on . . . ." (Borchert, Tr. at 353:1-21, A-5584; TE 110 at NV-0200007, A-8171.)

36. In the January 14, 2004 e-mail message, Mr. Garbell wrote, "[p]lease note that even with the comparative testing, I cannot promise success. However, without it, our chances of success are remote." (TE 110 at NV-0200007, A-8171.)

37. Novozymes initially followed Option 2, choosing to "stall" and "buy time" in which to carry out Option 1 and perform the allegedly comparative experiments. (TE 110 at NV-0200006, A-8170.) Novozymes' purpose in pursuing the plan to "buy time" was ultimately to obtain issuance of broader claims that would cover competitors' products, such as Genencor's SPEZYME® Ethyl. (Borchert, Tr. at 354:21-355:4, A-5585–5586; Garbell, Tr. at 427:5-428:2, A-5658–5659, 428:7-14, A-5659.)

38. Novozymes filed an amendment on January 14, 2004, to narrow the claims by adding the additional substitutions. In the amendment, Novozymes did not challenge the Examiner's *prima facie* finding of obviousness. (Borchert, Tr. at 352:18-25, A-5583; TE 101 at 593-597, A-7633–7637.)

39. Novozymes initiated experimental work giving rise to Dr. Borchert's Declaration under 37 C.F.R. § 1.132 (the "Borchert Declaration") in January or February 2004. (Borchert, Tr. at 365:9, A-5596.) As Dr. Borchert knew, the results of the testing were to be submitted to the PTO to overcome the rejection of the claims over Suzuki. (Borchert, Tr. at 354:21-355:4, A-5585–5586.) Yet, at the time the alleged experimental results were submitted to the PTO, there was no pending rejection based on Suzuki (or any other prior art reference). (Garbell, Tr. at 428:3-6, A-5659.)

40. Dr. Borchert was also informed by Mr. Garbell that all experimental results would have to be submitted to the PTO. (Garbell, Tr. at 431:13-18, A-5662, 435:2-13, A-5666.)

(4) Novozymes' Intensified Prosecution of the '031 Patent in Light of SPEZYME® Ethyl's Introduction

41. Novozymes heard about Genencor's launch of SPEZYME® Ethyl (*see* FF 51-59, below) in early 2004. (LeFebvre, Tr. 618:4-6, A-6026.) Many of Novozymes' customers began buying SPEZYME® Ethyl and stopped buying Novozymes' product, Liquozyme SC, because SPEZYME® Ethyl had higher performance and a competitive price. (LeFebvre, Tr. 620:21-22, A-6028.)

42. Nonetheless, Novozymes told its customers that it would reduce its prices while SPEZYME® Ethyl was on the market, but would raise its prices if it succeeded in removing SPEZYME® Ethyl from the market. (LeFebvre, Tr. at 622:20-24, A-6030.)

43. By August 2004, Novozymes had obtained samples of SPEZYME® Ethyl and sequenced at least the region containing the deletion of residues 179 and 180. (TE 516, A8901–8902.) An e-mail dated August 11, 2004 from Dr. Borchert stated "thanks for verifying the deletion of the two expected/feared amino acids." (Borchert, Tr. at 377:11-378:23, A-5608–5609; TE 516, A-8901–8902.)

44. In the same August 11, 2004 e-mail, after confirming the deletion of residues 179 and 180 in SPEZYME® Ethyl, Dr. Borchert wrote, "we are going for patent coverage of this deletion - as well - full speed." (Borchert, Tr. at 377:24-378:25, A-5608–5609; TE 516, A-8901–8902.)

(5) The '031 Patent Issues as a Result of Novozymes' Plan

45. Mr. Garbell and Dr. Borchert conducted a personal interview with the Examiner on September 3, 2004. At that time, there was no outstanding prior art rejection based on Suzuki and the Bisgard-Frantzen PCT. (Garbell, Tr. at 428:3-6, A-5659.) The purpose of the interview was to present to the Examiner a draft declaration of Dr. Borchert containing allegedly comparative data, to convince her to allow broad claims that would cover the 179-180 deletion in Genencor's product, which broad

claims had been earlier blocked by the Suzuki and Bisgard-Frantzen PCT prior art. In an Examiner-Initiated Interview Summary dated September 3, 2004, Examiner Prouty wrote that at the interview, they had "[d]iscussed the showing of unexpected results in the draft declaration and claim amendments. Examiner indicated that declaration does appear to show results sufficiently unexpected to overcome the previous 103 rejection of claims of similar scope to the draft claims." (Borchert, Tr. at 380:13-381:6, A-5611–5612; TE 101 at 758-759, A-7798–7799.)

46. On September 7, 2004, Dr. Borchert and Mr. Garbell submitted the Borchert Declaration to the PTO in connection with an amendment under 37 C.F.R. § 1.111. In the amendment, Novozymes did not challenge the Section 112 rejection of the narrowed claims (submitted under "Option 2"), the only rejection that was actually pending at that time. Novozymes also did not challenge the *prima facie* case of obviousness that the Examiner had set forth in the OA dated July 29, 2003. Instead, Novozymes, following Option 1, took back the earlier narrow claims and offered broader claims, based on alleged unexpected results. Mr. Garbell stated that "[a]s concluded by Dr. Borchert, these results were very surprising and unexpected in that they were significantly and substantially greater than what one of ordinary skill in the art would have expected, at the time the claimed invention was made, based on the collective teachings of the cited prior art." (Borchert, Tr. at 381:7-20, A-5612; TE 101 at 693-716, A-7733–7756; TE 508, A-8857–8874.)

47. Novozymes had not disclosed Machius '95 to the PTO, nor did it compare the alleged "unexpected results" to the teachings of Machius '95. (*See* FF 60.) There is no evidence in the prosecution history of the '031 Patent that the Examiner was aware of Machius '95 during the interview or that Machius '95 was before the Examiner when she considered whether to allow the asserted claims.

48. The PTO mailed a Notice of Allowance on September 21, 2004. In the accompanying Notice of Allowability, the Examiner provided the following reasons for allowance:

> [w]hile claims 48 and 50-52 would appear to be *prima facie* obvious over Suzuki *et al.* (JBC 260:6518, 1989) in view of Bisgard-Frantzen *et al.* (WO95/10603) as explained in the rejection of previous claims 30-33, 35 and 37-39 in the Office Action mailed, 7/29/03, the declaration of Dr. Torben Borchert submitted 9/7/04 establishes that the claimed variants exhibit unexpected large increases in thermostability when compared to the increases in thermostability obtained for the corresponding mutations taught by Suzuki *et al.* As such the claimed variants are non-obvious over the prior art.

(TE 101 at 756, A-7796.)

49. Novozymes contacted Genencor in writing with a copy of the allowed claims the day it submitted the '031 Patent issue fee. (Garbell, Tr. at 13:23-14:11, A-5013–5014.)

50. The '031 Patent issued on March 15, 2005. (TE 100 at 1, A-7001.) Novozymes filed suit against Genencor that same day. (Complaint, D.I. 1, A-1501–1542.)

D. **Background Regarding SPEZYME® Ethyl**

51. Genencor began selling SPEZYME® Ethyl in the United States by April of 2004, (Uncontroverted Facts at X), before the '031 Patent issued, before the asserted claims were allowed, and even before those claims were presented to the PTO. (FF 45-50.)

52. SPEZYME® Ethyl alpha-amylase enzyme is a protein of 484 amino acids with the following amino acid sequence:

> AAPFNGTMMQYFEWYLPDDGTLWTKVANEANNLSSLGIT
> ALWLPPAYKGTSRSDVGYGVYDLYDLGEFNQKGTVRTKY
> GTKAQYLQAIQAAHAAGMQVYADVVFDHKGGADGTEWV
> DAVEVNPSDRNQEISGTYQIQAWTKFDFPGRGNTYSSFKW
> RWYHFDGVDWDESRKLSRIYKFIGKAWDWEVDTENGNYD
> YLMYADLDMDHPEVVTELKNWGKWYVNTTNIDGFRLDA
> VKHIKFSFFPDWLSYVRSQTGKPLFTVGEYWSYDINKLHNY
> ITKTNGTMSLFDAPLHNKFYTASKSGGAFDMRTLMTNTLM
> KDQPTLAVTFVDNHDTEPGQALQSWVDPWFKPLAYAFILT
> RQEGYPCVFYGDYYGIPQYNIPSLKSKIDPLLIARRDYAYGT
> QHDYLDHSDIIGWTREGVTEKPGSGLAALITDGPGGSKWM
> YVGKQHAGKVFYDLTGNRSDTVTINSDGWGEFKVNGGSV
> SVWVPRKTT.

(Uncontroverted Facts at ¶ Z, A-1144–1145; Jorgensen, Tr. at 72:5-7, A-5072; TE 125, A-8345.)

53. SPEZYME® Ethyl is produced in Bra7, a strain of *Bacillus licheniformis*. (TE 194 at 6, A-8522.)

54. The DNA sequence from which Genencor obtains SPEZYME® Ethyl has changed over time. Until August 7, 2005, the sole DNA sequence from which SPEZYME® Ethyl was obtained ("Original DNA Sequence") was:

ATGAAACAACAAAAACGGCTTTACGCCCGATTGCTGACG
CTGTTATTTGCGCTCATCTTCTTGCTGCCTCATTCTGCAGC
TTCAGCAGCCGCACCGTTTAACGGTACCATGATGCAGTA
TTTTGAATGGTACTTGCCGGATGATGGCACGTTATGGAC
CAAAGTGGCCAATGAAGCCAACAACTTATCCAGCCTTGG
CATCACCGCTCTTTGGCTGCCGCCCGCTTACAAAGGAAC
AAGCCGCAGCGACGTAGGGTACGGAGTATACGACTTGTA
TGACCTCGGCGAATTCAATCAAAAAGGGACCGTCCGCAC
AAAATATGGAACAAAAGCTCAATATCTTCAAGCCATTCA
AGCCGCCCACGCCGCTGGAATGCAAGTGTACGCCGATGT
CGTGTTCGACCATAAAGGCGGCGCTGACGGCACGGAATG
GGTGGACGCCGTCGAAGTCAATCCGTCCGACCGCAACCA
AGAAATCTCGGGCACCTATCAAATCCAAGCATGGACGAA
ATTTGATTTTCCCGGGCGGGGCAACACCTACTCCAGCTTT
AAGTGGCGCTGGTACCATTTTGACGGCGTTGACTGGGAC
GAAAGCCGAAAATTAAGCCGCATTTACAAATTCATCGGC
AAAGCGTGGGATTGGGAAGTAGACACAGAAAACGGAAA
CTATGACTACTTAATGTATGCCGACCTTGATATGGATCAT
CCCGAAGTCGTGACCGAGCTGAAAAACTGGGGGAAATG
GTATGTCAACACAACGAACATTGATGGGTTCCGGCTTGA
TGCCGTCAAGCATATTAAGTTCAGTTTTTTTCCTGATTGG
TTGTCGTATGTGCGTTCTCAGACTGGCAAGCCGCTATTTA
CCGTCGGGGAATATTGGAGCTATGACATCAACAAGTTGC
ACAATTACATTACGAAAACAAACGGAACGATGTCTTTGT
TTGATGCCCCGTTACACAACAAATTTTATACCGCTTCCAA
ATCAGGGGGCGCATTTGATATGCGCACGTTAATGACCAA
TACTCTCATGAAAGATCAACCGACATTGGCCGTCACCTT
CGTTGATAATCATGACACCGAACCCGGCCAAGCGCTGCA
GTCATGGGTCGACCCATGGTTCAAACCGTTGGCTTACGC
CTTTATTCTAACTCGGCAGGAAGGATACCCGTGCGTCTTT
TATGGTGACTATTATGGCATTCCACAATATAACATTCCTT
CGCTGAAAAGCAAAATCGATCCGCTCCTCATCGCGCGCA
GGGATTATGCTTACGGAACGCAACATGATTATCTTGATC
ACTCCGACATCATCGGGTGGACAAGGGAAGGGGTCACTG
AAAAACCAGGATCCGGGCTGGCCGCACTGATCACCGATG
GGCCGGGAGGAAGCAAATGGATGTACGTTGGCAAACAA
CACGCTGGAAAAGTGTTCTATGACCTTACCGGCAACCGG
AGTGACACCGTCACCATCAACAGTGATGGATGGGGGGA

ATTCAAAGTCAATGGCGGTTCGGTTTCGGTTTGGGTTCCT
AGAAAAACGACCGTTTCTACCATCGCTCGGCCGATCACA
ACCCGACCGTGGACTGGTGAATTCGTCCGTTGGACCGAA
CCACGGTTGGTGGCATGGCCT

(TE 194 at 6-7, A-8522–8523.)

55. After August 7 and until September 2, 2005, SPEZYME® Ethyl was obtained variously from the Original DNA Sequence and from the following sequence ("New DNA Sequence"):

ATGAAACAACAAAAACGGCTTTACGCCCGATTGCTGACG
CTGTTATTTGCGCTCATCTTCTTGCTGCCTCATTCTGCAGC
TTCAGCAGCCGCACCGTTTAACGGTACCATGATGCAGTA
TTTTGAATGGTACTTGCCGGATGATGGCACGTTATGGAC
CAAAGTGGCCAATGAAGCCAACAACTTATCCAGCCTTGG
CATCACCGCTCTTTGGCTGCCGCCCGCTTACAAAGGAAC
AAGCCGCAGCGACGTAGGGTACGGAGTATACGACTTGTA
TGACCTCGGCGAATTCAATCAAAAAGGGACCGTCCGCAC
AAAATATGGAACAAAAGCTCAATATCTTCAAGCCATTCA
AGCCGCCCACGCCGCTGGAATGCAAGTGTACGCCGATGT
CGTGTTCGACCATAAAGGCGGCGCTGACGGCACGGAATG
GGTGGACGCCGTCGAAGTCAATCCGTCCGACCGCAACCA
AGAAATCTCGGGCACCTATCAAATCCAAGCATGGACGAA
ATTTGATTTTCCCGGGCGGGGCAACACCTACTCCAGCTTT
AAGTGGCGCTGGTACCATTTTGACGGCGTTGACTGGGAC
GAAAGCCGAAAATTAAGCCGCATTTACAAATTCATCGGC
AAAGCGTGGGATTGGGAAGTAGACACAGAAAACGGAAA
CTATGACTACTTAATGTATGCCGACCTTGATATGGATCAT
CCCGAAGTCGTGACCGAGCTGAAAAACTGGGGGAAATG
GTATGTCAACACAACGAACATTGATGGGTTCCGGCTTGA
TGCCGTCAAGCATATTAAGTTCAGTTTTTTTCCTGATTGG
TTGTCGTATGTGCGTTCTCAGACTGGCAAGCCGCTATTTA
CCGTCGGGGAATATTGGAGCTATGACATCAACAAGTTGC
ACAATTACATTACGAAAACAAACGGAACGATGTCTTTGT
TTGATGCCCCGTTACACAACAAATTTTATACCGCTTCCAA
ATCAGGGGGCGCATTTGATATGCGCACGTTAATGACCAA
TACTCTCATGAAAGATCAACCGACATTGGCCGTCACCTT
CGTTGATAATCATGACACCGAACCCGGCCAAGCGCTGCA
GTCATGGGTCGACCCATGGTTCAAACCGTTGGCTTACGC
CTTTATTCTAACTCGGCAGGAAGGATACCCGTGCGTCTTT
TATGGTGACTATTATGGCATTCCACAATATAACATTCCTT
CGCTGAAAAGCAAAATCGATCCGCTCCTCATCGCGCGCA
GGGATTATGCTTACGGAACGCAACATGATTATCTTGATC
ACTCCGACATCATCGGGTGGACAAGGGAAGGGGTCACTG
AAAAACCAGGATCCGGGCTGGCCGCACTGATCACCGATG
GGCCGGGAGGAAGCAAATGGATGTACGTTGGCAAACAA
CACGCTGGAAAAGTGTTCTATGACCTTACCGGCAACCGG

AGTGACACCGTCACCATCAACAGTGATGGATGGGGGGA
ATTCAAAGTCAATGGCGGTTCGGTTTCGGTTTGGGTTCCT
AGAAAAACGACCTGA

(TE 194 at 7-9, A-8523–8525.)

56. Since September 2, 2005, SPEZYME® Ethyl has been solely obtained from the New DNA Sequence. (TE 194 at 9, A-8525.) Novozymes has not offered any expert testimony or opinion as to infringement by SPEZYME® Ethyl as manufactured (based on the New DNA Sequence) after September 2, 2005. (Arnold Tr. at 187:14-188:5, A-5188–5189.)

57. SPEZYME® Ethyl was originally engineered from DNA encoding an alpha-amylase obtained from strain ATCC No. 39,709, which is also known as strain "G997." (Crabb, Tr. at 46:10-13, A-5046; TE 194 at 9, A-8525.)

58. The sequence of the protein encoded by the G997 alpha-amylase DNA is:

VLTFHRIIRKGWMFLLAFLLTASLFCPTGQHAKAAAPFNGT
MMQYFEWYLPDDGTLWTKVANEANNLSSLGITALWLPPA
YKGTSRSDVGYGVYDLYDLGEFNQKGTVRTKYGTKAQYL
QAIQAAHAAGMQVYADVVFDHKGGADGTEWVDAVEVNP
SDRNQEISGTYQIQAWTKFDFPGRGNTYSSFKWRWYHFDG
VDWDESRKLSRIYKFRGIGKAWDWEVDTENGNYDYLMYA
DLDMDHPEVVTELKNWGKWYVNTTNIDGFRLDAVKHIKF
SFFPDWLSYVRSQTGKPLFTVGEYWSYDINKLHNYITKTNG
TMSLFDAPLHNKFYTASKSGGAFDMRTLMTNTLMKDQPTL
AVTFVDNHDTEPGQALQSWVDPWFKPLAYAFILTRQEGYP
CVFYGDYYGIPQYNIPSLKSKIDPLLIARRDYAYGTQHDYL
DHSDIIGWTREGVTEKPGSGLAALITDGPGGSKWMYVGKQ
HAGKVFYDLTGNRSDTVTINSDGWGEFKVNGGSVSVWVP
RKTTVSTIARPITTRPWTGEFVRWTEPRLVAWP

(TE 194 at 9, A-8525.)

59. Genencor's development work leading up to SPEZYME® Ethyl started at least as early as 2002. (Crabb, Tr. at 31:24-32:5, A-5031–5032.) Genencor made the deletions at the relevant RG positions based on the teachings of Suzuki. (Crabb, Tr. at 40:11-41:7, A-5040–5041.) Dr. Crabb explained that Suzuki's teachings provided Genencor with the impetus to make the 179-180 deletion in a *Bacillus stearothermophilus* alpha-amylase. (Crabb, Tr. at 40:11-41:7, A-5040–5041.)

E. **Machius '95**

(1) Publication

60. The "Machius '95" reference, "Crystal Structure of Calcium-depleted *Bacillus licheniformis* α-amylase at 2.2 Å Resolution," was authored by Mischa Machius, Georg Wiegand, and Robert Huber (a Nobel Prize winner), and was published in the Journal of Molecular Biology, volume 246, pages 545-559, at least as early as March 13, 1995 ("Machius '95"). Machius '95 describes, *inter alia*, the crystal structure of an alpha-amylase from *Bacillus licheniformis.* (TE 173 at cover page and page 545, A-8375–8376; Machius, Tr. at 450:4-18, A-5681, 468:8-19, A-5699.)

61. As described above, the earliest possible effective priority date in the '031 Patent is March 29, 1995. (FF 20-23.) Machius '95 is prior art to the '031 Patent under 35 U.S.C. § 102(a).

(2) Background to Disclosure of Machius '95

(a) *X-ray crystallography*

62. X-ray crystallography is a method to determine the three-dimensional structures of molecules. In performing X-ray crystallography, a protein is crystallized, then the crystals are exposed to X-rays to generate a diffraction pattern. From the diffraction pattern, one can calculate the electron density, which shows where the amino acids are in the protein structure. The representation of the amino acid locations, *i.e.*, the three-dimensional structure, can be represented by numbers called the "atomic coordinates," which are reported in a file called a "protein data bank" or "PDB" file. (Machius, Tr. at 452:16-454:24, A-5683–5685.)

(b) *Protein structure*

63. Protein structure is characterized by primary, secondary, and tertiary structure. "Primary structure" is the amino acid sequence. "Secondary structure" consists of local structures that the amino acids fall into, such as alpha-helices and beta-strands. "Tertiary" or "three-dimensional" structure describes how the secondary structures come together in three dimensions to form the

specific shape of the protein molecule. (Machius, Tr. at 455:6-457:12, A-5686–5688, 458:17-461:5, A-5689–5692.)

64. The three-dimensional structure of a protein determines its properties. (Borchert, Tr. at 21:1-7, A-5021.) The three-dimensional structure of a protein also defines its function. (Machius, Tr. at 457:13-22, A-5688.)

65. A protein engineer would have known in 1995 that there are three-dimensional structural features that have been associated with the thermostability of proteins. (Machius, Tr. at 458:5-10, A-5689.)

66. For example, a protein engineer would have known in 1995 that proteins generally begin to unfold at weak regions in their structure. These regions are often in exposed surface loops. (Machius, Tr. at 461:16-462:2, A-5692–5693.)

67. Shorter loops are a prominent structural feature in the proteins that are more thermostable; a protein engineer in 1995 would have expected that a protein which had longer loops would have decreased thermostability. (Machius, Tr. at 461:16-463:18, A-5692; TE 178 at 185, A-8513.) The Vielle and Zeikus review (published in 1996 but based on work in 1995) states that "[l]oops are typically the regions with the largest thermal factors in a protein structure, indicating that they are likely to unfold first during thermal denaturation." (Machius, Tr. at 461:16-463:18, A-5692–5694; TE 178 at 187, A-8513.)

(3) Machius '95 Contains Substantial Teachings Not in Suzuki

68. Suzuki investigates why BLA is more thermostable than BAN. While Suzuki investigates the alignment of BLA and BAN and detects differences in the sequences, Suzuki does not disclose any secondary or tertiary structural information, or provide any structural explanation for the role of the deletion at positions 179-180, which are within what Suzuki labels as "Region I."

(Machius, Tr. at 464:12-23, A-5695; TE 115, A-8233–8238.) Suzuki does not teach that Region I of BLA is in a surface loop. (Machius, Tr. at 464:24-465:12, A-5695–5696.)

69. Suzuki does not compare the sequences of BLA and BAN to BSG, though such sequence comparisons were available in the literature. Even though it would have been reasonable to expect that these amylases would have similar three-dimensional structures, sequence comparisons would not tell one that a particular secondary or structural feature existed at any particular position. (Machius, Tr. at 465:13-466:4, A-5696–5697; TE 115, A-8233–8238.)

70. Machius '95 summarizes the findings of Suzuki. (TE 173 at 553, A-8384.)

71. In addition, Machius '95 teaches, beyond Suzuki, that the three-dimensional structures of BAA and BSG can be expected to be very similar to that of BLA. (Machius, Tr. at 472:6-11, A-5703; TE 173 at 553, A-8384.)

72. Machius '95 further teaches, beyond Suzuki, that Region I in BLA is a loop on the surface of domain B. (Machius, Tr. at 472:12-20, A-5703; TE 173 at 553, A-8384.)

73. Machius '95 teaches, beyond Suzuki, that "[t]his loop is enlarged in BAA by two extra residues which could cause increased mobility of this region and a decreased thermostability of the whole protein." (Machius, Tr. at 472:12-20, A-5703; TE 173 at 553, A-8384.)

74. In sum, Machius '95 contains teachings, not present in Suzuki, that the three-dimensional structures of BAN, BLA, and BSG would be expected to be very similar; that the region in BAN that contains Suzuki Region I is a surface exposed loop; and that BAN Region I is enlarged by two residues, which could be the reason why BAN has a reduced thermostability compared to BLA. (Machius, Tr. at 478:24-479:19, A-5709–5710.)

(4) Novozymes Admits that Machius '95 Contains Teachings Not in Suzuki

75. Dr. Borchert admitted that Suzuki does not teach the three-dimensional structures of the alpha-amylases, and, in particular, does not teach that Region I is in a surface loop. (Borchert, Tr. at 357:22-358:7, A-5588–5589.)

76. Dr. Borchert admitted that Suzuki does not teach that the three-dimensional structures of BAN, BLA, and BSG are expected to be similar. (Borchert, Tr. at 359:12-360:7, A-5590–5591.)

(5) Novozymes' Attacks on Machius '95 are Unfounded

(a) *The crystallization conditions do not affect the relevant teachings of Machius '95*

77. The Machius '95 paper states that the BLA alpha-amylase protein was crystallized in the absence of calcium (which is important for catalytic function), that the protein was cleaved after residue 189, and that the electron density could not be resolved between residues 182 and 192. These issues are discussed throughout the paper. (Machius, Tr. at 470:23-471:16, A-5701–5702, 472:21-473:4, A-5703–5704; TE 173, particularly at the Abstract, A-8376.)

78. The lack of metal bound to the structure, cleavage of the protein, and unresolved electron density in certain areas do not take away from the unqualified conclusion expressed in Machius '95 that Suzuki Region I is in a surface loop. In addition, the electron density for the residues of Suzuki Region I was well-resolved, as reported in Machius '95. (Machius, Tr. at 471:17-22, A-5702, 472:21-473:7, A-5703–5704; TE 173, A-8375–8390.)

(b) *Machius '95 does not "take back" its express conclusion that Region I is in a surface loop*

79. The statement in Machius '95 indicating that "[n]one of the above-mentioned theories is able to explain satisfactorily the enhanced thermostability of BLA," refers to the previously published work of other authors, such as that of Suzuki, not the conclusions reached and findings reported by

Machius and co-authors as expressly stated in Machius '95. (Machius, Tr. at 476:10-477:7, A-5707–5708; TE 173 at 553, A-8384.)

(c) *The atomic coordinates were not necessary to understand the core teachings of Machius '95*

80. Machius '95 indicates on page 557 (in the "acknowledgements" section) that "[t]he [atomic] co-ordinates have been deposited with the Brookhaven Protein Data Bank and will be released with a delay of two years, and are available from the authors on request in the meantime." If protein engineers or structural biologists wanted the coordinates in 1995, they could have gotten them. (Machius, Tr. at 477:15-478:17, A-5708–5709; TE 173 at 557, A-8388.)

81. Protein engineers do not typically publish the atomic coordinates along with their paper because of the data's length. (Machius, Tr. at 777:10-17, A-6565; TE 118, A-8251–8328.) For example, Novozymes, including inventors Borchert, Bisgard-Frantzen, and Svendsen, as well as Novozymes' expert Dr. Gideon Davies, published a paper on the crystal structure of a chimeric alpha-amylase, but did not include the atomic coordinates with the paper and did not release the coordinates until the next year after publication. (Machius, Tr. at 777:18-781:18, A-6565–6569; TE 102, A-8147–8156 and TE 103, A-8157–8168.)

82. One of ordinary skill in the art would not have needed the atomic coordinates to understand the teachings of Machius '95, including the teachings regarding three-dimensional structure, which went beyond the teachings of Suzuki. Machius '95 explicitly describes the relevant three-dimensional structure and includes several graphics and other representations that convey the core teachings. With respect to Region I, there are several graphical representations that show that Region I is in a loop, and there is an explicit statement to that effect. (Machius, Tr. at 478:18-23, A-5709, 508:2-14, A-5739, 776:1-17, A-6564.)

(6) Machius '98 Confirms the Core Teachings of Machius '95

83. In a subsequent publication, Dr. Machius and his colleagues determined the structure of BLA in the presence of calcium. This publication, which was authored by Dr. Machius, along with Nathalie Declerck, Robert Huber, and Georg Wiegand, was entitled "Activation of *Bacillus licheniformis* α-amylase through a disorder → order transition of the substrate-binding site mediated by a calcium-sodium-calcium metal triad," and published in the journal Structure, volume 6, pages 281-292 in 1998 ("Machius '98"). This protein was not cleaved and the areas that were not resolved in Machius '95 were resolved in Machius '98. This structure confirmed that Suzuki Region I is in a surface loop. (Machius, Tr. at 473:10-476:9, A-5704–5707; TE 175, A-8391–8402.)

(7) Machius '95 Makes the Claimed Invention Obvious

84. Machius '95 makes it obvious to one of ordinary skill in the art to make the 179 and 180 deletion in BSG. The information that the Suzuki Region I is in a surface loop increases the motivation for the ordinarily skilled artisan to make the mutation beyond the motivation provided by Suzuki. (Machius, Tr. at 484:1-485:6, A-5715–5716, 774:3-22, A-6562.)

85. While after Suzuki published his study, there was motivation to make the deletion in BSG (*see* Arnold, Tr. at 742:9-11, A-6530; *see also* Crabb, Tr. at 40:11-41:7, A-5040–5041), Suzuki hypothesizes about the presence of specific interactions in the Suzuki Region that would have been of concern to one considering making that mutation in BSG. The conclusion of Machius '95, that Suzuki Region I is in a surface loop, is important because loops do not have many interactions. A protein engineer would have realized this, and on reading Machius '95 would have had increased motivation to make the deletion in BSG. Dr. Machius testified that it would have been a "no-brainer." (Machius, Tr. at 774:3-22, A-6562.) No contradictory testimony was presented at trial.

(8) Novozymes Was Very Familiar with Machius '95, Especially During the Prosecution of the '031 Patent

86. Dr. Borchert admitted that he read Machius '95 closely soon after it was published. (Borchert, Tr. at 360:22-361:8, A-5591–5592.)

87. Dr. Borchert invited Dr. Machius to give a lecture at Novozymes in 1995 after Machius '95 was published. (Borchert, Tr. at 361:9-15, A-5592; Machius, Tr. at 468:20-469:1, A-5699–5700.)

88. In 1996, Dr. Borchert gave a lecture at an American Oil Chemists Society Meeting in Indianapolis, at which he indicated that Machius '95 provides the crystal structure of the BLA alpha-amylase. (Borchert, Tr. at 361:16-362:19, A-5592–5593; TE 664 at GCOR170281, A-9048.)

89. In 1997, Novozymes cited Machius '95 in a response to the PTO in connection with another patent application naming Dr. Borchert as an inventor, to support the patentability of the claims. (Borchert, Tr. at 363:6-365:1, A-5594–5596; TE 665 at NV-0094701, A-9065.)

90. In 2000, all three of the '031 Patent inventors, Drs. Borchert, Bisgard-Frantzen, and Svendsen, as well as Novozymes' expert Dr. Davies, published a paper on the crystal structure of a chimeric alpha-amylase in which they cite to Machius '95 in the abstract and at other pages. (TE 102 at 1, 4-5, A-8147, 8150–8151.) Citation to a reference in the abstract of a paper is unusual and indicates that the reference is of particularly high relevance and/or importance. (Machius, Tr. at 781:25-783:11, A-6569–6571; TE 102, A-8147–8156.) The '031 inventors and Dr. Davies relied on Machius '95 to report that the structure of BLA had been "determined" (TE 102 at 1, A-8147), meaning that the location of atoms in the molecule relative to each other had been solved. (Borchert, Tr. at 22:1-6, A-5022.)

91. Mr. Garbell was aware of Machius '95 during the '031 Patent prosecution. (Garbell, Tr. at 12:8-12, A-5012.) Mr. Garbell had reviewed Machius '95 in detail in connection with an interference proceeding pending during, and prosecuted in parallel with, the '031 Patent prosecution. (Garbell, Tr. at 426:11-22, A-5657.) Mr. Garbell and Dr. Borchert were working together on the

interference in which Machius '95 was discussed at the same time they were preparing the Borchert Declaration submitted in the '031 Patent prosecution. (Borchert, Tr. at 368:19-24, A-5599.)

92. Mr. Garbell and Dr. Borchert extensively discussed Machius '95 during the pendency of the application that issued as the '031 Patent. (Garbell, Tr. at 440:4-441:10, A-5671–5672 and 442:15-17, A-5673.)

93. Mr. Garbell knew that Machius '95 was relevant to prosecution of the '031 Patent. Mr. Garbell mentioned to Dr. Borchert that "I had noticed that Machius had summarized the prior art to include the Suzuki reference. And whenever I used the word Suzuki, I assumed Dr. Borchert made the connection of Suzuki to the '031 Patent…." (Garbell, Tr. at 440:23-441:2, A-5671–5672.)

94. On August 27, 2004, just before the September 3, 2004 examiner interview, Dr. Borchert submitted a declaration to the PTO in connection with the co-pending interference in which he discussed Machius '95. (Borchert, Tr. at 368:11-372:3, A-5599–5603; TE 524 at 13 ¶¶ 38 and 39, A-8915, and 14 ¶ 43, A-8916.) Shortly after the examiner interview, Dr. Borchert gave a deposition in the interference in which he testified concerning Machius '95. (Borchert, Tr. at 368:25-369:5, A-5599–5600.)

95. Machius '95 was not cited to the PTO during prosecution of the '031 Patent. Neither Mr. Garbell nor Dr. Borchert discussed Machius '95 with the Examiner during the September 3, 2004 interview. (Garbell, Tr. at 11:22-12:6, A-5011–5012, 429:2-11, A-5660; Borchert, Tr. at 372:7-15, A-5603; TE 101, A-7041–8146.)

96. Mr. Garbell was not a person of ordinary skill in the art of protein engineering during prosecution of the '031 Patent. (Garbell, Tr. at 425:22-426:6, A-5656–5657; *see* FF 6.)

97. During prosecution of the '031 Patent, Mr. Garbell was aware of the "when in doubt" rule concerning disclosure of material information, including the general guidance that, "when in

doubt" as to materiality, an applicant should submit information to the Examiner. (Garbell, Tr. at 431-19-432:5, A-5662, 444:23-445:14, A-5675–5676.)

98. Mr. Garbell admitted that had Novozymes disclosed Machius '95 in prosecution, there was a possibility that the '031 Patent would not have issued. (Garbell, Tr. at 445:9-14, A-5676.)

99. The Examiner cited Machius '95 in the parent application of the '031 Patent after the issue fee had been paid in the '031 Patent application. However, Novozymes made no attempt to pull the '031 Patent from issuance in order to cite Machius '95 in the '031 Patent prosecution. (Garbell, Tr. at 430:9-431:12, A-5661–5662.)

F. **The Borchert Declaration and Alleged "Experiment"**

100. Novozymes submitted alleged unexpected results to support the issuance of broader claims. These alleged unexpected results were presented by comparison to Suzuki, even though the rejection based on Suzuki was not pending when the results were submitted and had not been pending for several months. The alleged unexpected results were submitted in order to take back the narrowing claims (offered as "Option 2") and obtain broader claims specifically targeted to Genencor, and were obtained from an experiment that was, at the least, substantially deficient. Moreover, Novozymes reporting of the alleged results was misleading and fraudulent.

101. In addition, the Borchert Declaration was ultimately misleading because it presented alleged unexpected results in comparison to Suzuki, which was not the closest prior art. *See* Manual of Patent Examining Procedure ("MPEP") §§ 716.02(b)-(e); *Ex parte Ishizaka*, 24 U.S.P.Q. 2d 1621, 1624 (Bd. Pat. App. & Interf. 1992). In fact, the closest prior art was Machius '95, of which Novozymes was fully aware during the '031 Patent's prosecution, but which was never disclosed to the PTO or compared to the so-called "unexpected results."

(1) Summary of the "Experiment" and Reported Conclusions

102. Enzyme thermal inactivation assays such as those described in the Borchert Declaration entail heating an aqueous solution of the enzyme, periodically withdrawing samples from heat, and measuring their residual activity in an enzyme activity assay. (Klibanov, Tr. at 516:13-21, A-5747.) The alpha-amylase enzyme activity assay involves monitoring the cleavage of starch from a complex of starch and blue dye; the complex is colorless but as the starch is cleaved some of the blue dye becomes soluble and produces a blue color in solution. Enzyme activity is reflected in the intensity of the blue color of the solution in an amylase activity assay. (Klibanov, Tr. at 514:13-25, A-5745.) One can plot the residual activity as a function of time of heating to determine the time required to halve the activity of the enzyme. (Klibanov, Tr. at 516:21-24, A-5747, 515:7-9, A-5746.) This time is called the "half-life." (Klibanov, Tr. at 515:19-25, A-5746.)

103. The Borchert Declaration described experiments allegedly measuring the thermal inactivation of several enzymes: BAN WT, BAN del, BSG WT, and BSG del; based on these measurements, Dr. Borchert calculated half-lives for each of the enzymes. To calculate the alleged improvement in the thermostability of BAN upon introduction of the Suzuki deletion, Dr. Borchert divided the half-life of BAN del by the alleged half-life of BAN WT and "found" it to be 11. Similarly, to calculate the alleged improvement in the thermostability of BSG upon introduction of the Suzuki deletion, Dr. Borchert divided the half-life of BSG del by the half-life of BSG WT and found the improvement to be 63. Dr. Borchert then calculated an alleged relative improvement in BSG to BAN upon introduction of the Suzuki deletion of 63 ÷ 11, or 5.7. (Klibanov, Tr. at 521:9-522:13, A-5752–5753; TE 508 at ¶ 7, A-8860.)

(2) There Were Numerous Differences Between the Borchert "Experiment" and Suzuki

104. The thermal inactivation assays described in the Borchert Declaration were conducted at 80°C, whereas the Suzuki studies had been conducted at 90°C (Borchert, Tr. at 382:4-9, A-5613), even though Suzuki determines a half-life for BAN WT at 90°C. (TE 115 at 18937, A-8237.)

105. In the thermal inactivation assays of Suzuki, the enzyme whose thermostability was being tested was added to preheated (or "prewarmed") buffer (TE 115 at 18934, left column, under heading "*Heat Inactivation of the α-amylases*," A-8234.) in order to avoid a ramp-up period. (Klibanov, Tr. at 514:14-24, A-5745.) Dr. Borchert never did so in the experiments submitted to the PTO by way of his Declaration. (Borchert, Tr. at 397:4-7, A-5628; TE 508 at ¶ 5, A-8858.) Preheating the buffer in a thermal inactivation assay has been a universal, standard practice for more than 30 years. (Klibanov, Tr. at 525:6-526:8, A-5756–5757.)

106. Unlike Suzuki's thermal inactivation experiments, which employed 10 mM calcium (TE 115 at 18934, A-8234, left column, under heading "*Heat Inactivation of the α-amylases*"), Dr. Borchert chose to employ a calcium concentration of 0.1 mM. (TE 508 at ¶ 5, A-8858.) As stated by Dr. Borchert, "[c]alcium is known to improve the stability of alpha amylases. So if you have an alpha-amylase that is not sufficiently stable, you can somehow circumvent that by adding high levels of calcium." (Borchert, Tr. at 26:17-22, A-5026.)

(3) Deficiencies in the "Experiment"

107. In addition to the numerous differences from Suzuki, the Borchert "experiment" suffered from numerous deficiencies, including the "ramp-up" period in the heating of BAN WT, improper extrapolation of half-life calculations, and omission of data points, as explained below.

(a) *Failure to account for ramp-up in heating of BAN WT*

108. In Dr. Borchert's experiments, a solution of enzyme was placed in a tube at room temperature, then the tube was placed in the heating device. As the enzyme was heating up to 80°C, its

pace of inactivation was slower than it was when the temperature of the solution reached 80°C. This period as the enzyme was heating up to 80°C was the "ramp-up" period. (Klibanov, Tr. at 523:21-524:11, A-5754–5755.)

109. The shorter the half-life of an enzyme, the more significant the ramp-up period. For example, in the case of BAN WT where the enzyme half-life is under one minute, a ramp-up period of half a minute that is unaccounted for makes a significant contribution to the calculated half-life of an enzyme. For enzymes with longer half-lives, such as those of BAN del, BSG, and BSG del, the half-minute ramp-up period makes very little, if any, contribution to the calculated half-life. (Klibanov, Tr. at 604:7-605:9, A-6012–6013.)

110. As shown above (FF 104-106), even though Novozymes presented "unexpected results" as compared to Suzuki, there were numerous differences between the Borchert "experiment" and the experiment reported in Suzuki. Novozymes does not dispute that fact. Rather, in "response," Novozymes' expert Dr. Arnold merely alleged that industrial protocols for measuring the half-lives of BSG enzymes, including BSG del, do not include a step for preheating the buffer. (Arnold, Tr. at 750:17-21, A-6538, 750:23-754:6, A-6538–6542.) Even if this were true, however, it does not change the undisputed fact that the Borchert "experiment" and Suzuki differed in this important respect (which Novozymes did not disclose to the Examiner). Moreover, the limited evidence Novozymes did present of industrial testing established that pre-heating the buffer is routine. (Crabb, Tr. at 52:21-53:13, A-5052–5053.)

111. As a consequence of Dr. Borchert's failure to account for the ramp-up period, the half-life of BAN WT presented in the Borchert Declaration is greatly overestimated, and the BAN improvement is underestimated. (Klibanov, Tr. at 527:18-528:3, A-5758–5759.) Specifically, Dr. Klibanov, using the data in the Borchert Declaration, but appropriately accounting for the ramp-up period, estimated the half-life of BAN WT under the conditions of the Borchert Declaration to be

approximately 0.3 minutes (as compared to the 0.9 minutes presented in the Borchert Declaration). (Arnold, Tr. at 765:8-25, A-6553.)

112. Novozymes attempted to address the "ramp-up" issue by conducting new experiments during the litigation. The half-life for BAN WT calculated based on the data from Novozymes' new experiments was as little as 0.435 minutes. (Arnold, Tr. at 749:1-19, A-6537, 764:15-24, A-6552, 765:23-25, A-6553; TE 208-R, A-8541–8542.)

113. It is not clear that even the new litigation-driven experiments were reliable. Using a protocol provided by Darby and Darby (Tams, Tr. at 636:21-637:2, A-6044–6045), experiments comparing the rate of inactivation of BAN WT using preheated and unheated buffer were performed by Jeppe Tams of Novozymes and his technician, Mette Egede. (Tams, Tr. at 634:1-13, A-6042.) However, Dr. Tams' testimony shows that he did not adhere to the protocol. (Tams, Tr. at 655:5-8, A-6063, 655:24-656:2, A-6063–6064, 656:6-9, A-6064.)

114. If reliable, Dr. Arnold's new calculation confirms that a "ramp-up" issue affected Novozymes' experiment and the Borchert Declaration. Dr. Arnold's calculated 0.435-minute half-life for BAN WT is far closer to Dr. Klibanov's calculation (approximately 0.3 minutes, accounting for ramp-up) than to Dr. Borchert's alleged calculation, of 0.9 minutes. (Arnold, Tr. at 749:1-19, A-6537, 764:15-24, A-6552, 765:23-25, A-6563; Klibanov, Tr. at 527:18-528:3, A-5758–5759; TE 208-R, A-8541–8542; *compare* TE 508 at 7, A-8863.)

115. Thus, failing to account for the "ramp-up" period resulted in inflating the half-life of BAN WT by a factor of 2 or more. This overestimation of the BAN WT half-life in the Borchert Declaration results in an overestimation of the relative improvement of BSG versus BAN upon introduction of the Suzuki deletion because it underestimates the improvement in BAN del compared to BAN WT. (Klibanov, Tr. at 527:18-528:3, A-5758–5759.) The true relative improvement, if reliably calculable, is discussed below.

(b) *BSG Del extrapolation*

116. Enzyme half-life is virtually impossible to directly measure, because one would have to be lucky enough to have taken a measurement when residual activity was precisely 50%. (Klibanov, Tr. at 517:4-9, A-5748.) Thus, generally one has to rely on interpolation, which is an estimation of half-life on the basis of residual activities below and above 50%. (Klibanov, Tr. at 517:4-9, A-5748.)

117. Dr. Borchert did not have any data measurements for BSG del that came near 50% residual activity; the closest alleged measurement was more than a day short of 50%. (Klibanov, Tr. at 530:10-13, A-5761.)

118. Thus, in order to calculate the half-life of BSG del, Dr. Borchert had to resort to extrapolation. (Klibanov, Tr. at 531:6-12, A-5762.) Extrapolation assumes that the rate of BSG del thermal inactivation follows first order kinetics, such that semilogarithmically plotting the residual activity versus time of heating would result in a straight line from which the time of 50% residual activity can be estimated. (Klibanov, Tr. at 531:13-532:1, A-5762–5763.)

119. There is no evidence that it was appropriate to assume first order kinetics were exhibited in the data and that, as a result, extrapolation would be appropriate. Dr. Borchert never tested or proved the apparent assumption that first order kinetics were obeyed. (Klibanov, Tr. at 532:6-9, A-5763.) In fact, Novozymes' litigation testing of BAN WT (*see* FF 112-114, above) show that thermal inactivation of that enzyme does not obey first order kinetics. (Klibanov, Tr. at 532:6-9, A-5763.) Moreover, nothing in the data itself indicates that the thermal inactivation of BSG del follows first order kinetics. (Klibanov, Tr. at 533:20-534:5, A-5764–5765.)

120. Therefore, it was inappropriate to extrapolate a half-life for BSG del. Because the half-life of BSG del was improperly extrapolated, it is unreliable. (Klibanov, Tr. at 533:13-14, A-5764.) As a consequence of the extrapolation, the half-life of BSG del presented in the Borchert Declaration may be overestimated, and, as a result, the relative improvement of BSG versus BAN upon

introduction of the Suzuki deletion may be overestimated and is unreliable. (Klibanov, Tr. at 534:16-535:2, A-5765–5766.)

(c) *Omitted data points*

121. The data in the Borchert Declaration was generated by Ms. Holbo, Dr. Borchert's technician. (Borchert, Tr. at 365:5-366:13, A-5596–5597.)

122. The Borchert Declaration does not contain data points measured for BSG del at 2881 minutes (Borchert, Tr. at 384:22-24, A-5615; TE 508 at ¶ 6, A-8859–8860) or at 2940 minutes. (Borchert, Tr. at 386:9-15, A-5617; TE 508 at ¶ 6, A-8859–8860.) Dr. Borchert testified that "we deliberately decided not to include those measurements in the final data" submitted to the PTO (Borchert, Tr. at 386:18-19, A-5617), and never brought up these data omissions during the interview with the Examiner. (Borchert, Tr. at 386:20-22, A-5617.)

123. Accordingly, the Borchert Declaration as filed with the PTO does not cite any established reason as to why the 2881 and 2940 data points in the BSG del series were omitted. (Klibanov, Tr. at 543:18-25, A-5774.) Rather, Dr. Borchert chose not to inform the Examiner that these data points had been omitted from the Declaration. (Borchert, Tr. at 396:16-17, A-5627.)

124. The omission (removal) of an experimental data point that is an outlier is scientifically improper, unless an established reason exists why the outlier occurred. "If a reason cannot be found, then the observation should not be removed from further analysis." (Klibanov, Tr. at 542:11-543:14, A-5773–5774, quoting from Milliken & Johnson, 2002, "Analysis of Messy Data.")

(i) The 2881 data points

125. Ms. Holbo testified that she did not withhold any results of her experimental work from Dr. Borchert, and that it was her intention to give Dr. Borchert all of the results from her experimental work underlying the Borchert Declaration. (Holbo, Tr. at 673:6-14, A-6081.)

126. Ms. Holbo testified that the sample from which the residual activity measurements at 2881 minutes were taken had evaporated. (Holbo, Tr. at 671:6-9, A-6079.) Ms. Holbo testified that the measurements at 2881 minutes were "not okay" because she made a notation that these values were "read to the curve" (Holbo, Tr. at 676:17-19, A-6084), but could not explain what this meant. (Holbo, Tr. at 678:1-4, A-6086.)

127. Normally, when a sample has evaporated it was Ms. Holbo's practice to redo the experiment. (Holbo, Tr. at 669:9-12, A-6077.) However, in this instance, Ms. Holbo analyzed the residual activity of the sample and calculated its value at 56%, but told the statistician, Mr. Poulsen, not to use the data in his half-life calculations. (Holbo, Tr. at 671:10-14, A-6079, 678:13-16, A-6086.)

128. According to Dr. Klibanov, Novozymes' explanation for the omission of the 2881 data points is unsatisfactory; if the sample had evaporated, then the enzyme solution would have become more concentrated, and resulted in an activity reading that was higher than expected, instead of an activity reading that is lower than expected, which was what was observed by Novozymes. (Klibanov, Tr. at 537:5-17, A-5768.)

(ii) The 2940 data points

129. In the course of residual activity measurements, loose substrate occasionally is present when taking measurements, distorting them. (Holbo, Tr. at 672-3-11, A-6080.) It was Ms. Holbo's practice to indicate with parentheses that an experimental measurement has excess substrate from the enzyme activity assay. (Holbo, Tr. at 672:12-13, A-6080, 676:14-17, A-6084.)

130. Of the two data points at 2940 minutes of heating omitted by Dr. Borchert from his Declaration, only one had been marked in parentheses by Ms. Holbo. However, there was no conceivable reason for Dr. Borchert to omit the other experimental point at 2940 minutes, which Ms. Holbo testified was "fine." (Holbo, Tr. at 681:15-17, A-6089.) Indeed, two other data points in

parentheses were omitted from the BSG WT half-life calculations in the Borchert Declaration, whereas their good counterparts made their way into the Declaration. (Klibanov, Tr. at 538:15-20, A-5769.)

131. The omission of the legitimate data point at 2940 minutes from the calculations of the Borchert Declaration inflated the calculated half-life of BSG del, and hence overestimated the relative improvement of BSG versus BAN. (Klibanov, Tr. at 540:9-14, A-5771.)

(4) Accounting for "Ramp-Up" or Not, the "Manipulated Results" Were Not Surprising to One of Skill in the Art

132. Dr. Borchert testified that one of ordinary skill in the art could not have a specific expectation of the increase in thermostability in BSG relative to the increase in thermostability of BAN upon introduction of that same deletion. (Borchert, Tr. at 410:10-19, A-5641.)

133. As described above, the data and conclusions reported in the Borchert Declaration are so unreliable and incomplete that it is not possible to calculate a "true" relative increase in thermostability between BAN WT/BAN del and BSG WT/BSG del. Even taking the Borchert data at face value and calculating the relative improvement in BSG versus BAN upon introduction of the Suzuki deletion, the difference in improvement in BSG versus BAN was under a factor of two. (Klibanov, Tr. at 549:7-8, A-5780, 610:3-11, A-6018.) This would not be surprising to one of skill in the art, because the relative magnitude of improvement is so low. (Klibanov, Tr. at 549:7-8, A-5780, 545:15-549:7, A-5776–5780, 610:3-11, A-6018–6019.)

134. Independently, in view of Suzuki, whose data show approximately a 25-fold improvement in thermostability of BAN upon the deletion, one of ordinary any skill in the art would not have been surprised by Dr. Borchert's results with BSG WT/BSG del because the improvement observed was in the same order of magnitude as the observed improvement in BAN. (Klibanov, Tr. at 545:15-549:7, A-5776–5780; TE 115 at Fig. 1, Fig. 5, and 18935, A-8234, A-8237, and A-8235.)

G. The '031 Patent Prosecution History Defines "Parent *Bacillus stearothermophilus* Alpha-amylase" as "SEQ. ID NO:3"

135. The '031 Patent provides several alternative definitions of the term "parent." The specification most narrowly defines the term "parent α-amylase" as an alpha-amylase with the amino acid sequence of SEQ ID NO:3. However, the specification also recites that a "parent" may be an alpha-amylase that is at least 80% homologous to SEQ ID NO:3 (*i.e.*, may have an amino acid sequence that differs by up to 20% from the sequence of SEQ ID NO:3) or, even more broadly, an alpha-amylase that is bound by an antibody that binds to a protein having the amino acid sequence of SEQ ID NO:3 or that is encoded by DNA that hybridizes to DNA encoding the amino acid sequence of SEQ ID NO:3. (TE 100 at col. 7:18-8:30, A-7011.)

136. During prosecution, Novozymes initially had claims pending that defined the parent alpha-amylase as having a certain percent homology to SEQ ID NO:3 and not reciting any percent homology between the parent and the variant. (TE 101 at 5-7, A-7045–7047.)

137. The Examiner rejected those claims under 35 U.S.C. § 112 as lacking written description and enablement in the OA dated July 29, 2003. The Examiner suggested that the rejection could be overcome by specifying that the variant alpha-amylase had a certain percent homology to SEQ ID NO:3. (TE 101 at 583-87, A-7623–7627.)

138. In an amendment dated January 14, 2004, Novozymes amended the claims but did not follow the Examiner's suggestion. Instead, Novozymes amended the claims to require that the variant have a certain percent homology with respect to its parent. (TE 101 at 594-95, A-7634–7635.)

139. In response, in an OA dated April 6, 2004, the Examiner rejected all these claims as too broad, stating, *inter alia*, that the specification did not enable a variant that is at least 80% identical to a parent that is at least 80% to 95% identical to SEQ ID NO:3. According to the Examiner, the claims pending at that time encompassed alpha-amylases with an enormous number of variations not enabled by the few examples in the specification. The Examiner did indicate that the specification enabled

variant alpha-amylases having at least 90% homology to SEQ ID NO:3. Thus, the Examiner indicated that the variant should be defined by its percent homology to SEQ ID NO:3, and not to the "parent," which was too broad. (TE 101 at 679-86, A-7719–7726.)

140. In the September 7, 2004 amendment, Novozymes canceled all claims and added new claims, which issued as claims 1-5 of the '031 Patent. New claim 48, which issued as claim 1, recited a "variant" that has 95% homology to the "parent," without specifying any degree of homology between the parent and SEQ ID NO:3. In setting out the support for the new claims, however, Novozymes cited to the third and fifth paragraphs on page 10 of the specification, which Novozymes characterized in the amendment as "describing variants of *Bacillus stearothermophilus* and variants having at least 95% homology to SEQ ID NO:3." The passages cited by Novozymes, corresponding to the '031 Patent, 7:32-35 and 7:41-51 (TE 100 at 11, col. 7:32-35, 7:41-51, A-7011), refer only to SEQ ID NO:3 and not to any broader definition of "parent." (TE 101 at 694-95, A-7734–7735.)

141. In addition, Novozymes asserted that the new claims comported with the Examiner's suggestion to define the variants with respect to SEQ ID NO:3. In the September 7, 2004 amendment, Novozymes argued:

> The Office concluded that although these [previous] claims are enabled for alpha-amylase variants having 90% homology to SEQ ID NO.3, that [*sic*] these claims lack enablement for alpha-amylase variants having 80% or 85% homology to SEQ ID NO. 3.
>
> Applicants respectfully submit that this rejection is rendered moot by the new claims as the new claims recite a homology of 95%.

(TE 101 at 695-96, A-7735–7736.)

142. In that same amendment, Novozymes explicitly stated that "[t]he presently claimed invention is directed to variants of *Bacillus stearothermophilus* alpha-amylase enzymes and to alpha-amylase variants having 95% homology to SEQ ID NO:3." (TE 101 at 696, A-7735.)

H. **The '031 Patent and Other Evidence Support the Conclusion that "*Bacillus stearothermophilus* Alpha-amylase" Means "the Full-length Protein Encoded by the *Bacillus stearothermophilus* Gene, Minus the Signal Sequence"**

143. As discussed above, while the '031 Patent does not provide an express definition of "*Bacillus stearothermophilus* alpha-amylase," that term should mean "SEQ ID NO:3." Alternatively, that term should mean "a 514-515 amino acid alpha-amylase encoded by a wild type *Bacillus stearothermophilus* gene, minus the signal sequence," as explained below.

(1) Every *Bacillus stearothermophilus* Alpha-amylase Mentioned in the '031 Patent Has 514 or 515 Amino Acids

144. The '031 Patent cites a publication by Gray *et al.*, 1986, J. Bacteriol. 166:635-643 (TE 629, A-9003–9012), as the source of a suitable parent *Bacillus stearothermophilus* alpha amylase. (Alber, Tr. at 222:18-223:9, A-5223–5224; TE 100 at 11, col. 7:32-35, A-7011.) The Gray *et al.* paper shows in Figure 2b that the wild type *Bacillus stearothermophilus* alpha-amylase described has 515 amino acids. (Alber, Tr. at 223:3-20, A-5224; TE 629 at 4, A-9006.)

145. The '031 Patent contains Figure 1, which lists various alpha-amylase sequences. (TE 100 at 3, A-7003.) The second line throughout the table that is labeled "3" is a *Bacillus stearothermophilus* alpha-amylase having 514 amino acids. (Alber, Tr. at 223:22-224:9, A-5224–5225; TE 100 at 11, col. 7:32-34, A-7011.)

146. The '031 Patent contains a "sequence listing" having an amino acid sequence, designated "SEQ ID NO:3," of a third *Bacillus stearothermophilus* alpha-amylase, which has 514 amino acids. (Alber, Tr. at 224:11-24, A-5225; TE 100 at 30-32, cols. 45-50, A-7030–7032.)

147. Thus, all examples of the *Bacillus stearothermophilus* alpha-amylases in the '031 Patent have either 514 or 515 amino acids. (Alber, Tr. at 221:25-226:9, A-5224–5227.)

(2) All *Bacillus stearothermophilus* Alpha-amylases Reported In The Literature as of 1995 Had 514 or 515 Amino Acids

148. In 1995, a protein engineer would have considered the term "*Bacillus stearothermophilus* alpha-amylase" to mean the full-length preprotein encoded by a wild type *Bacillus stearothermophilus* alpha-amylase gene, modified by removal of the signal sequence as the protein is secreted from the cell. (Alber, Tr. at 206:9-13, A-5207.) Specifically, a protein engineer in 1995 would have expected a wild type *Bacillus stearothermophilus* alpha-amylase to have a total of 514 or 515 amino acids, depending on the strain from which the gene was isolated. (Alber, Tr. at 208:11-17, A-5209, 272:22-273:12, A-5503–5504.)

149. The understanding of a skilled protein engineer in 1995 would have been based on the literature as of 1995 describing wild type *Bacillus stearothermophilus* alpha-amylase genes and the corresponding mature alpha-amylase proteins that were reported to have been produced from such genes as of 1995. (Alber, Tr. at 208:18-24, A-5209, 277:14-21, A-5508.)

150. Ihara *et al.*, 1985, J. Biochem. (Tokyo) 98(1):95-103 (TE 628, A-8993–9002), published in 1985, states that the *Bacillus stearothermophilus* alpha-amylase gene of wild type strain DY-5 encodes a preprotein of 548 amino acids, which is processed in *Bacillus stearothermophilus* to a mature alpha-amylase of 514 amino acids by removal of the N-terminal signal sequence. (Alber, Tr. at 209:2-18, A-5210, 209:25-210:5, A-5210–5211; TE 628 at 1, Abstract and 2, A-8993–8994.)

151. Gray *et al.*, 1986, J. Bacteriol. 166:635-643 (TE 629, A-9003–9012), published in 1986, states that *Bacillus stearothermophilus* wild type strain NZ-3 isolated from the Rotorua thermal area of New Zealand (TE 629 at 1, col. 2, A-9003) encodes a mature alpha-amylase of 515 amino acids after removal of the signal sequence from the larger "precursor" protein. (Alber, Tr. at 211:6-212:3, A-5212–5213; TE 629 at 3, para. bridging columns, A-9005.) This publication by Gray *et al.* is referenced in the '031 Patent as the source of a suitable parent *Bacillus stearothermophilus* alpha-amylase. (TE 100 at 11, col. 7:32-35, A-7011.)

152. Suominen *et al.*, in *Proceeding of an International Symposium on Extracellular Enzymes of Microorganisms,* September 1-5, 1987, Plenum Press, New York, Chaloupka and Krumphanzl eds., pp. 129-137 (TE 630, A-9013–9024), published in 1987, states that the sequence of an alpha-amylase gene isolated from *Bacillus stearothermophilus* wild type strain ATCC 12980 encodes a mature protein of 515 amino acids after removal of the signal sequence from the "preprotein." (Alber, Tr. at 212:19-214:8, A5213–5215; TE 630 at 6, Fig. 2 and its legend, A-9018.)

153. Nakajima *et al.*, 1985, J. Bacteriol. 163(1):401-406 (TE 568, A-8943–8950), published in 1985, states that the gene for a *Bacillus stearothermophilus* alpha-amylase encodes a protein of 549 amino acids; removal of the signal sequence *in vivo* yields a mature protein of 515 amino acids. (Alber, Tr. at 212:19-214:8, A-5213–5215; TE 568 at 2, Abstract, A-8944.)

154. Jorgensen *et al.*, 1991, FEMS Microbiol. Lett. 77: 271-276 (TE 142, A-8359–8364), published in 1991, states that the sequence of an alpha-amylase gene in the *Bacillus stearothermophilus* wild type strain DN1792 produces a 549 amino acid protein with a "mature part of 515 amino acids." (Alber, Tr. at 212:19-214:8, A-5213–5215; TE 142 at 4, col. 2, A-8362.)

155. Tsukagoshi *et al.*, 1984, Mol. Gen. Genet. 193:58-63 (TE 633, A-9025–9030), published in 1984, states that the experimentally observed molecular weight of the *Bacillus stearothermophilus* alpha-amylase of the wild type strain DY-5 is 61,000 Da. (Alber, Tr. at 212:19-214:8, A-5213–5215; TE 633 at 1, Summary, A-9025.)

156. Tsukagoshi *et al.*, 1985, J. Bact. 164:1182-1187 (TE 634, A-9031–9036), published in 1985, states that the experimentally observed molecular weight of the *Bacillus stearothermophilus* alpha-amylase of the wild type strain DY-5 is 60,000 Da. (Alber, Tr. at 212:19-214:8, A-5213–5215; TE 634 at 4, col. 1, A-9034.)

157. Egelseer *et al.*, 1995, J. Bact. 177:1444-1451 (TE 635, A-9037–9044), published in 1995, states that the experimentally observed molecular weight of the *Bacillus stearothermophilus*

alpha-amylase of the wild type strain DSM 2358 is 58,000 Da. (Alber, Tr. at 212:19-214:8, A-5213–5215; TE 635 at 1, Abstract, A-9037.)

158. Those papers above, which published molecular weights of the alpha-amylases (*e.g.*, TE 633, A-9025–9030, TE 634, A-9031–9036, and TE 635, A-9037–9044), base those molecular weights on experiments using "gels." (Alber, Tr. at 274:22-25, A-5505.) Novozymes' Dr. Jorgensen used such methods to calculate molecular weights, which proved consistent with molecular weights obtained by mass spectrometry. (Alber, Tr. at 277:10-23, A-5508.)

159. The Vihinen paper, published in 1995, demonstrates that in 1995 a protein engineer would have been able to distinguish between a *Bacillus stearothermophilus* alpha-amylase having amino acids 1-515 and one having amino acids 1-498, and among these two proteins and one having amino acids 1-483. (Alber, Tr. at 220:23-221:14, A-5221–5222.) The Vihinen paper reports that its authors could tell the difference on a "gel" between the full-length protein and its truncated products that differed from each other by about 15 or 17 amino acids. (Alber, Tr. at 275:16-276:4, A-5506–5507.) Based on this experimental evidence in the Vihinen paper, a skilled protein engineer in 1995 would have accepted the conclusions of Tsukagoshi *et al.* (TE 633, A-9025–9030), Tsukagoshi *et al.* (TE 634, A-9031–9036), and Egelseer *et al.* (TE 635, A-9037–9044) that they had experimentally observed alpha-amylases having 514 or 515 amino acids, and would have concluded that they were not observing truncated forms of those proteins having on the order of 484 amino acids.

160. The pages printed from Genbank website for Accession Numbers AAB86961 (1997), AAU10478 (2005), ABC18196 (2006), and CAB93517 (2001) (TE 666, at 1, 4, 8, and 10, respectively, A-9085, 9088, 9092, and 9094), list amino acid sequences of alpha-amylase preproteins from wild type *Bacillus stearothermophilus* strains. All are consistent with there being a "full-length," 514- or 515-amino acid alpha-amylase after removal of the signal sequence from the preprotein. (Alber, Tr. at 214:13-215:12, A-5215–5216; TE 666, A-9085–9096.)

161. In sum, all literature as of 1995, and later publications, report that the sequence of a mature alpha-amylase was 514 or 515 amino acids. As Dr. Alber testified, "[e]very paper I could find since, before 1995 and since 1995, when a sequence of a mature alpha-amylase was listed it was listed as either 514 or 515 amino acids." (Alber, Tr. at 215:9-12, A-5216.)

162. The definition based on the literature as of 1995 that a "*Bacillus stearothermophilus* alpha-amylase" is a 514- or 515-amino acid protein encoded by a wild type *Bacillus stearothermophilus* alpha-amylase gene, minus the signal sequence, is consistent with the teachings of the '031 Patent, since as shown above (FF 144-147) all examples of the *Bacillus stearothermophilus* alpha-amylases in the '031 Patent have either 514 or 515 amino acids. (Alber, Tr. at 221:25-226:9, A-5222–5227.)

163. The protein engineer's definition as of 1995 of a "*Bacillus stearothermophilus* alpha-amylase" as a 514- or 515-amino acid protein encoded by a wild type *Bacillus stearothermophilus* alpha-amylase gene, minus the signal sequence, is consistent with the amino acid sequence of SEQ ID NO:3 of the '031 Patent, which has a total of 514 amino acids and is encoded by a *Bacillus stearothermophilus* alpha-amylase gene. (Alber, Tr. at 244:6-22, A-5245.)

164. Thus, there is nothing in the '031 Patent or the literature that is inconsistent with the teaching that a *Bacillus stearothermophilus* alpha-amylase gene encodes a 514- or 515-amino acid protein, after removal of the signal sequence. (Alber, Tr. at 224:25-225:6, A-5225–5226.)

165. Dr. Jorgensen's conclusion that his sequencing of Genencor's G-ZYME® G997 alpha-amylase commercial product revealed a truncation at its C-terminus is not evidence that one of ordinary skill in the art as of 1995 would have thought that a "*Bacillus stearothermophilus* alpha-amylase" would have such a truncation, because the data was not available in 1995 for consideration by a protein engineer. (Alber, Tr. at 225:13-226:5, A-5226–5227; Jorgenson, Tr. at 663:20-23, A-6071.)

166. Even if the data was available, a protein engineer as of 1995 would not have considered the evidence presented by Dr. Jorgensen of the sequence of G-ZYME® G997 to be proof of the structure of a wild type, naturally occurring *Bacillus stearothermophilus* alpha-amylase. (Alber, Tr. at 228:6-11, A-5229.) In part, this is because there was no evidence in the published literature as of 1995 of any naturally occurring *Bacillus stearothermophilus* alpha-amylases with a truncation at the C-terminus, as Dr. Arnold admitted. (FF 148-161, 167.)

(3) Novozymes' Expert Agreed that a Protein Engineer in 1995 Would Have Expected a *Bacillus stearothermophilus* Alpha-amylase to Have 514 or 515 Amino Acids

167. Novozymes' expert, Dr. Arnold, testified that in 1995 a skilled protein engineer would have expected an alpha-amylase expressed from an alpha-amylase gene of a wild type *Bacillus stearothermophilus* to have 514 or 515 amino acids. (Arnold, Tr. at 180:1-6, A-5181.) Dr. Arnold also admitted that as of March 1995, there was no evidence in the published literature of any alpha-amylase expressed from a wild type *Bacillus stearothermophilus* gene that was truncated at its C-terminus. (Arnold, Tr. at 180:7-12, A-5181.)

(4) The Protein of Genencor's G-ZYME® G997 Commercial Product is Not a "*Bacillus stearothermophilus* Alpha-amylase"

168. Novozymes apparently asserts that Genencor's product G-ZYME® G997 (a fermentation product of the *Bacillus stearothermophilus* strain G997) is the "parent *Bacillus stearothermophilus* alpha-amylase" to which SPEZYME® Ethyl should be compared to evaluate infringement of '031 Patent claims 1, 3, and 5. This assertion is incorrect.

(a) *Novozymes' litigation sequencing of G-ZYME® G997*

169. The G-ZYME® G997 amino acid sequence obtained by Novozymes during this litigation for sample "TS1855S," also called "PA6064," is found in TE 199. (Jorgensen, Tr. at 71:16-21, A-5071; TE 206 at 4, ¶ 17, A-8539.1.) As reported by Novozymes, that amino acid sequence is

486 amino acids long and ends with the amino acids, KTT. (Jorgensen, Tr. at 71:16-21, A-5071; Alber, Tr. at 301:20-302:2, A-5532–5533; TE 206 at 4, ¶ 17, A-8539.1.)

170. Dr. Jorgensen admitted that he could not say that all samples of G-ZYME® G997 would have the same protein sequence, and further admitted that he could not say that the protein sequence of G-ZYME®G997 is always the same. (Jorgensen, Tr. at 80:18-21, A-5080, 83:10-13, A-5083, 83:23-25, A-5083.)

(b) *Genencor's pre-litigation sequencing of G-ZYME® G997*

171. A Genencor research technician (Crabb, Tr. at 50:13-18, A-5050; Alber, Tr. at 256:8-11, A-5257), Judy Chang, wrote a report, dated April 19, 2004 (before the '031 Patent was allowed or issued, and before the claims at issue were presented to the PTO), describing the results of Genencor's sequencing of its G-ZYME® G997 product. (Alber, Tr. at 249:13-17, A-5250; TE 161, A-8365–8374.) Ms. Chang reported that the G-ZYME® G997 product included multiple alpha-amylases of different lengths—there were three different deletions at the C-terminus. (Alber, Tr. at 249:13-17, A-5250, 280:6-19, A-5511, 286:11-14, A-5517, 291:12-292:9, A-5522–5523; TE 161, A-8365–8374.) Ms. Chang reported a mixture of three protein sequences, variously with 27, 28, and 29 amino acids deleted at the C-terminus. (Alber, Tr. at 280:6-19, A-5511, 302:10-14, A-5533.) Referring to Figure 3 of Ms. Chang's report (TE 161 at 5, A-8369), those three sequences had different endings at the C-terminus (KTTVS, KTTV, and KTT), and were different lengths (488, 487, and 486 amino acids).

(c) *Genencor's G-ZYME® G997 commercial product is not a "Bacillus stearothermophilus alpha-amylase" because it has substantial deletions at the C-terminus*

172. The alpha-amylase gene of *Bacillus stearothermophilus* strain G997 encodes a mature alpha-amylase of 515 amino acids. (TE 161 at 4, A-8368.)

173. As described above, sequencing by both Novozymes and Genencor shows that Genencor's G-ZYME® G997 product has a truncation in C-terminus from the 515-amino acid

preprotein encoded by the alpha-amylase gene of *Bacillus stearothermophilus* strain G997, *i.e.*, it is missing from the C-terminus at least 27, 28, or 29 amino acids. (*See* FF 169-171.) For that reason alone, it is not a "*Bacillus stearothermophilus* alpha-amylase" as understood by a protein engineer as of 1995, because it is not a 514- or 515-amino acid alpha-amylase. (Alber, Tr. at 249:23-250:4, A-5250–5251, 260:25-261:12, A-5261–5262.)

174. Additionally, the G-ZYME® G997 commercial product is also not a "parent *Bacillus stearothermophilus* alpha-amylase" within the meaning of the '031 Patent, because it is the product of an industrial process. (Alber, Tr. at 249:23-250:4, A-5250–5251, 260:25-261:12, A5261–5262.)

(5) No Fermentation Product Can Be the "Parent *Bacillus stearothermophilus* Alpha-amylase" of the '031 Patent

(a) *Industrial conditions cause sequence differences*

175. Even when one begins a fermentation with a known gene, one cannot be certain what will be the amino acid sequence of the ultimate protein that results from the fermentation of an organism expressing that gene (the "fermentation product"). (Alber, Tr. at 227:11-14, A-5228.) This is because, once the protein encoded by the gene is made, there is a lot that can happen to it; for example, when one breaks the cells, the proteins from the inside and outside of the cells all mix together and the protein encoded by the gene is exposed to enzymes, called proteases, that can cut the protein chain. (Alber, Tr. at 227:15-21, A-5228.)

176. The G-ZYME® G997 commercial product is the result of an industrial fermentation process, which could provide an explanation for deletions at the C-terminus. (Alber, Tr. at 226:6-9, A-5227.) The fermentation processes used to make industrial proteins are very harsh and would likely lead to post-translational modifications, such as the cutting of the C-terminus. (Alber, Tr. at 226:9-12, A-5227.)

177. Since the G-ZYME® G997 commercial product contains multiple alpha-amylase proteins, it is a "moving target" in terms of its sequence because it has heterogeneity at its C-terminus. (Alber, Tr. at 260:6-16, A-5261, 262:20-263:2, A-5263–5264, 279:13-280:5, A-5510–5511.)

(b) *Expression in different systems of alpha-amylases encoded by the same DNA can lead to sequence differences*

178. The alpha-amylase protein encoded by the gene of strain ATCC 31,195 and strain G997 are identical. However, when Dr. Jorgensen sequenced various product proteins expressed from those genes in a fermentation, the product proteins were different. (Jorgensen, Tr. at 661:15-19, A-6069; Alber, Tr. at 230:20-231:4, A-5231–5232.)

179. Specifically, Dr. Jorgensen presented evidence of his sequencing of an alpha-amylase expressed in *Bacillus subtilis* (Jorgensen, Tr. at 664:9-11, A-6072) from the gene of the *Bacillus stearothermophilus* strain, ATCC 31,195. (Alber, Tr. at 229:7-13, A-5230; TE 135, A-8357.) When that sequence is compared to Dr. Jorgensen's sequence of the alpha-amylase of one sample of Genencor's G-ZYME®G997 product (TE 123, A-8343), the sequences are different—the alpha-amylase of strain ATCC 31,195 is three amino acids longer than the alpha-amylase of Genencor's G-ZYME®G997 product. (Alber, Tr. at 229:15-230:4, A-5230–5231, 286:14-17, A-5517.) (Note that the sequence of TE 123 ends with the amino acids KTT, while the sequence of TE 135 ends with the amino acids KTTVST.)

180. Dr. Jorgensen also presented evidence of a sequencing of an alpha-amylase expressed in *Bacillus stearothermophilus* (Jorgensen, Tr. at 664:16-19, A-6072) from DNA of the *Bacillus stearothermophilus* strain, ATCC 31,195. (Jorgensen, Tr. at 657:13-22, A-6065, 658:4-11, A-6066, 659:21-660:4, A-6067–6068; TE 201, A-8531.) This alpha-amylase ended with the amino acids KTTVS (Jorgensen, Tr. at 663:2-4, A-6071; TE 201, A-8531), whereas the alpha-amylase of TE 135 (based on the same DNA, from strain ATCC 31,195, but expressed in *Bacillus subtilis*) ended with the amino acids KTTVST. (Jorgensen, Tr. at 662:24-663:1, A-6070–6071; TE 135, A-8357.) These two

product protein sequences were different, even though they were expressed from the same DNA. (Jorgensen, Tr. at 663:5-7, A-6071.)

181. Dr. Jorgensen's work shows that, if one expresses a protein from the same *Bacillus stearothermophilus* alpha-amylase DNA in different *Bacillus* strains, the ultimate fermentation products protein can vary at the C-terminus. (Jorgensen, Tr. at 663:8-19, A-6071.)

182. Moreover, the amino acid sequences of both of those product alpha-amylases from the ATCC 31,195 gene are different from the amino acid sequence reported by Dr. Jorgensen for samples of Genencor's G-ZYME®G997 product. (Compare TE 201, A-8531 and TE 135, A-8357 with TE 123, A-8343; Alber, Tr. at 301:17-302:14, A-5532–5533.)

183. Thus, although the genes of strain ATCC 31,195 and strain G997 encode the same mature protein, the different conditions of fermentation or sample handling led to different C-terminus ends, and therefore different sequences, for the two protein products. (Alber, Tr. at 230:25-231:4, A-5231–5232.) It is normal that there would be differences between such product proteins as a result of fermentation and industrial processing, because different processes can produce different post-translational modifications. (Alber, Tr. at 231:15-21, A-5232.)

184. Thus, the product protein of G-ZYME®G997 cannot be the "parent" or "*Bacillus stearothermophilus* alpha-amylase" of the '031 Patent.

(c) *Unlike a product protein, the mature protein encoded by the parent gene does not vary and provides a certain basis for comparison*

185. There was no evidence available to one of skill in the art in 1995 that there was any uncertainty about the length of the "mature" protein encoded by a *Bacillus stearothermophilus* alpha-amylase gene (minus the removal of the signal sequence from the preprotein). (Alber, Tr. at 226:20-227:4, A-5227–5228, 232:9-11, A-5233, 303:4-9, A-5534.) It is always 514 or 515 amino acids and independent of the conditions of a fermentation in which it is expressed because it is defined by the